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# Gone but Not Forgotten: Lesional Memory in Psoriatic Skin

Rachael A. Clark[1]

**One of the most frustrating aspects of treating psoriasis is the tendency of psoriatic skin lesions to recur after therapy has been discontinued. Not only do lesions recur, but they often recur in the same anatomical locations, expanding to the size they were before therapy. This engenders feelings of frustration and futility in both patients and the dermatologists who care for them. In this issue, Suárez-Fariñas and colleagues identified a gene set—the residual disease genomic profile—of psoriasis, suggesting the presence of both immunologic and structural abnormalities within healed psoriatic lesions. By understanding this "invisible lesion," we may be one step closer to curing psoriasis.**

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Psoriatic skin lesions are a "riot" of disorder, featuring dense inflammatory cell infiltrates, massive proliferation, impaired differentiation of the epidermis, formation of new blood vessels, and alterations in lymphatic structure. With effective therapy, psoriatic lesions resolve without scarring. This lack of scarring is remarkable, given the number of neutrophils in psoriatic skin lesions and the scarring observed in other neutrophil-mediated disorders, including pyoderma gangrenosum. Successful treatment of psoriasis leads to resolution of epidermal thickness, reduced numbers of inflammatory cells, and return of previously affected skin to a clinically normal state (Chamian *et al*., 2005; Zaba *et al*., 2007).

Once therapy is discontinued, psoriatic skin lesions tend to recur, usually at the same sites that were affected previously. Clearly, something marks the boundary of healed psoriatic lesions that leads inflammation to recur in these places. Understanding and repairing the residual lesion in treated psoriatic skin may mean the difference between treating psoriasis and curing it.

In this issue, Suárez-Fariñas and coinvestigators address this important question. This group studied patients who had responded clinically and histologically to therapy with the TNF-α antagonist etanercept. Previously lesional but now normal-appearing skin was sampled, and three types of studies were performed. First, microarray and RT-PCR analyses were used to evaluate gene expression. The authors zeroed in on a set of previously identified psoriasis-associated genes and determined which normalized after therapy and which did not. A distinct set of genes remained abnormally expressed in healed lesional skin. The authors refer to this gene set as the residual disease genomic profile of psoriasis. These genes can be divided into two functional categories. Microarray studies demonstrated that a panel of inflammation-related genes remained elevated in treated lesions, including lymphotoxin and the T-cell receptor β1 chain. These two genes are both products unique to T cells, and their persistent elevation suggests the continued presence and activation of T cells in resolved lesions. RT-PCR studies confirmed elevated levels of IL-12p35, IL-22, IL-17, and IFN-γ, products of genes that are related to the presence and stimulation of IL-17–producing T cells. A second set of genes with persistently abnormal expression mapped to structural cell types within the skin. These included genes expressed in lymphatic vessels and within the epidermis. Taken together, these studies suggest a continuing presence of both immunologic and structural abnormalities within healed psoriatic lesions.

Suárez-Fariñas *et al.* (2011) then performed a series of histologic studies to determine whether they could link gene expression alterations to observable changes within the skin. They found that a population of $CD8^+$ T cells remained present in the dermis of treated lesions, a striking finding given the number of T-cell-related genes that remained abnormally expressed. Second, they observed persistent changes in the morphology and gene expression of lymphatic vessels. Expression of the gene LYVE-1 was persistently downregulated in healed psoriatic lesions as compared with normal skin. In normal skin, lymphatic channels expressing this gene were located in the upper reticular dermis and had wide, open lumens. In active and healed psoriatic lesions, these vessels were more collapsed and were located higher in the skin, closer to the dermal–epidermal junction. Although T cells and other inflammatory cells use blood vessels to enter skin, they use lymphatic vessels to leave it. By restricting egress of inflammatory cells from skin, persistent lymphatic abnormalities could contribute to recurring inflammation. Abnormal lymphatics alone should not cause inflammation, but they may amplify and prolong inflammation from other sources.

What then is the signature remaining in resolved psoriatic lesions? As scientists, it is critical that we be aware of our own biases. The truth lies in the experimental findings themselves, not in the hypotheses we formulate to explain them. This is the cornerstone of good science and, indeed, good medicine. Admittedly, I think that most of the pathology in skin is caused by T cells. Despite this bias, the data do suggest that a persistent presence and activation of $CD8^+$ T cells may mark the territory of psoriatic lesional skin and could be responsible for the recurrence of lesions in the same anatomical sites.

[1]*Harvard Skin Disease Research Center and Department of Dermatology, Brigham and Women's Hospital, Boston, Massachusetts, USA*

*Correspondence: Rachael A. Clark, EBRC 505A, 221 Longwood Avenue, Boston, Massachusetts 02115, USA. E-mail: rclark1@partners.org*

One of the most significant ideological shifts in the field of cutaneous immunology has been the realization that effector T cells generated by local immune responses persist long-term within the skin and that they can provide protection against local rechallenge by pathogens (Clark, 2010; Gebhardt *et al*., 2009; Liu *et al*., 2010). At least a subset of these cells are sessile and nonmigratory, remaining fixed in location within the skin (Gebhardt *et al*., 2009). We as cutaneous immunologists have been peppered for years by insightful questions about why lesions of psoriasis, fixed drug eruption, and mycosis fungoides recur at the same sites. It is possible that we are beginning to understand this phenomenon.

Mycosis fungoides is a form of cutaneous T-cell lymphoma in which malignant T cells are localized to fixed patches and plaques of inflamed skin. The lesions appear to resolve with topical steroid therapy but often recur in the same sites and regrow to their previous size. We have recently found that the malignant T cells in mycosis fungoides have the phenotype of effector memory T cells ($T_{EM}$), a cell type that has been shown in mouse models to be nonmigratory (Campbell *et al*., 2010). In contrast, the malignant T cells in Sézary syndrome have the phenotype of cutaneous central memory cells ($T_{CM}$), a cell type that in mouse models recirculates among the skin, blood, and lymph nodes. It appears that these two forms of cutaneous T-cell lymphoma represent malignancies arising from two different T-cell subsets and that the malignant T cells in these disorders maintain the migratory behaviors of their benign precursors. This would explain why patients with mycosis fungoides have fixed plaques that recur in the same locations and do not experience spread of malignant T cells into the blood or other tissues. It would also explain why patients with Sézary syndrome have erythroderma as opposed to fixed plaques (because the malignant T cells move within the skin), as well as accumulation of malignant T cells in the blood and lymph nodes.

Fixed drug eruption is an unusual cutaneous hypersensitivity response in which patients develop dusky, usually solitary, plaques of inflamed skin. Once the offending drug is removed, the lesions resolve. If the offending medication is taken again, years or sometimes decades later, patients develop a recurrence of their skin lesions, often at the same anatomic sites affected previously. This is another example of a recurrent cutaneous reaction most likely caused by nonmigratory skin resident T cells. Biopsy of resolved lesions of fixed drug eruption has demonstrated the continued presence of a distinct population of IFN-γ–producing $CD8^+$ T cells (Teraki and Shiohara, 2003). These investigators did not demonstrate directly that these T cells were specific for the offending medication, but their findings suggest that nonmigratory $CD8^+$ cells within these areas of skin are responsible for the fixed nature of this recurrent eruption.

> Understanding abnormalities in healed psoriatic skin moves us one step closer to curing psoriasis.

Accumulating evidence suggests that psoriasis is an autoimmune T-cell–mediated disorder, and recent studies have highlighted the importance of IL-17–producing T cells and activated dermal antigen-presenting cells in this process (Blauvelt, 2007; Lowes *et al*., 2007; Nickoloff, 2007). Because the dermis of healed psoriatic skin lesions is persistently colonized by a population of $CD8^+$ T cells, it is possible that these lesion-resident $CD8^+$ T cells may be the long sought-after autoreactive T-cell population in psoriasis. Indeed, $CD8^+$ T cells producing IL-17 are found in psoriatic skin lesions but not in normal skin (Kryczek *et al*., 2008). It is tempting to speculate that a nonmigratory population of autoreactive IL-17–producing $CD8^+$ T cells is responsible for the fixed nature of psoriatic skin lesions and that the waxing and waning activation state of these cells gives rise to the clinical variations in disease activity observed in patients.

It is possible, however, that structures distinct from T cells retain the memory of psoriatic lesions. Suárez-Fariñas *et al*. (2011) identify gene expression and morphologic changes in the lymphatic vessels of healed lesions that may exacerbate inflammation as a result of injury or other insults, leading to a low threshold for inflammation at the sites. They also identify changes in the gene expression of RAB31, a protein expressed by at least two populations of antigen-presenting cells in the skin. It is possible that psoriatic lesions are delineated by nonmigratory antigen-presenting cells that, by persistent presentation of immunogenic self-peptides, stimulate autoreactive T cells and induce inflammation selectively at these sites.

In summary, Suárez-Fariñas and colleagues (2011) have taken important steps toward understanding the immunologic and structural footprint that remains after the clinically visible inflammation of psoriasis has passed. By understanding and treating these invisible lesions, we may one day be able to give patients with psoriasis the gift they long for: truly normal skin.

## CONFLICT OF INTEREST

The author states no conflict of interest.

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# The Coordinated Response of the Physical and Antimicrobial Peptide Barriers of the Skin

Andrew W. Borkowski[1] and Richard L. Gallo[1]

**Antimicrobial peptides (AMPs) are an essential and multifunctional element for immune defense of the skin during infection and injury. In this issue, Ahrens *et al.* characterize the response of β-defensins, a class of AMPs, following acute and chronic challenges to the permeability barrier of the skin. Their findings suggest that the antimicrobial and permeability barriers of the skin are closely linked.**

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The multiple defensive functions of human skin depend on its ability to detect danger from a broad range of physical, chemical, and microbiological challenges, and they are interconnected to minimize the potential for damage. The skin's defensive functions are often thought of as acting through two simultaneously acting barriers, the immune antimicrobial barrier and the physical permeability barrier. Following physical injury to the skin, a cascade of events occurs to restore the breached skin barrier and reestablish homeostasis. In contrast, during infection, microbes encounter both the complex lipid and protein structures of the stratum corneum and an array of antimicrobial molecules that are already present or may be triggered by a set of pattern recognition receptors. In combination, these barriers typically act to facilitate the elimination of pathogens. In recent years, it has been shown that the pathways that generate and regulate the antimicrobial barrier of the skin are closely tied to pathways that modulate permeability barrier function (Dorschner *et al.*, 2001; Schauber *et al.*, 2007; Aberg *et al.*, 2007, 2008). In this issue, Ahrens *et al.* report that both acute and chronic skin barrier disruption lead to increased expression of murine β-defensins (mBDs)-1, -3, and -14 and that this increase in expression is diminished when the barrier is artificially restored. Their data contribute to the concept that the antimicrobial and permeability barriers of the skin are closely linked.

[1]*Division of Dermatology, Department of Medicine, University of California at San Diego and VA San Diego Health Care System, San Diego, California, USA*

*Correspondence: Richard L. Gallo, Division of Dermatology, Department of Medicine, University of California, San Diego, 9500 Gilman Drive, #0869, San Diego, California 92093, USA. E-mail: rgallo@ucsd.edu*

## Antimicrobial nature of the skin

The integrity of the skin barrier is essential for it to properly serve its purpose as a shield from the environment. Keratinocytes are at the forefront of this defense because they make up the majority of epidermal cells and are in constant contact with the outside world. Keratinocytes are responsible for producing the stratum corneum, the terminally differentiated outer layer of the epidermis composed of rigid, anucleate corneocytes cemented by hydrophobic, lipid-rich lamellar bilayers that impede water loss and protect from pathogenic organisms (reviewed in Candi *et al.*, 2005). Although keratinocytes serve as a physical barrier, they also express an array of molecules that contribute to the antimicrobial properties of skin (reviewed in Elias, 2007). A wide arsenal of weapons combats possible invaders via the skin. Constant desquamation of the skin makes it difficult for organisms to establish permanent residence. The surface of the skin is an acidic environment (pH ~ 5.5) uninhabitable to many microorganisms. Additionally, it has been suggested that the microflora that normally inhabit human skin can contribute to barrier defenses by competing for nutrients and niches that more pathogenic organisms require, by expressing antimicrobial molecules that kill or inhibit the growth of pathogenic microbes (Cogen *et al.*, 2010; Nakatsuji *et al.*, 2010), and by modulating the inflammatory response (Lai *et al.*, 2009).

Over the past decade, it has become increasingly apparent that keratinocytes and other resident skin cells produce a number of antimicrobial molecules important for maintaining homeostasis (Gallo and Huttner, 1998). Studies of antimicrobial peptides (AMPs) in many organ systems have shown them to engage in a wide range of activities including direct microbial killing,